Small effort, high impact: focus on physical activity improves oxygen uptake (VO_{2peak}), quality of life and mental health after pediatric renal transplantation

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Running head: Improved VO_{2peak} and QoL after renal tx

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Abbreviations: VO_{2peak}, oxygen uptake; QoL, quality of life; PedsQL, the pediatric quality of life inventory; SDQ, strength and difficulties questionnarie; ESRD, end stage renal disease; CVD, cardiovascular disease; HENT (health after kidney transplantation); ABPM, ambulatory blood pressure monitoring; RER, respiratory exchange rate; CR, cardiorespiratory; mGFR, measured glomerular filtration rate; SBP, systolic blood pressure; DBP diastolic blood pressure; HRQoL (health related quality of life; TAC tacrolimus, CsA cyclosporine; EVE everolimus; AZA, azathioprine.

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Abstract

This study estimates the effects on peak oxygen uptake ($VO_{2\ peak}$), quality of life (QoL) and mental health after the introduction of an adjusted post-transplant follow-up program, i.e. early physiotherapy and focus on the importance of physical activity. $VO_{2\ peak}$ was measured by a treadmill exercise test in 20 renal transplanted children on the adjusted post-transplant follow-up and compared with a group of 22 patients investigated in a previously, before the implementation of our new follow-up routines. The Pediatric Quality of Life Inventory (PedsQL) and The Strengths and Difficulties Questionnaire (SDQ) were used to assess QoL and mental health in 45 patients on the new as compared to 32 patients on the previous follow-up strategy.

The patients exposed to early physiotherapy and a higher focus on physical activity had significantly higher $VO_{2\ peak}$ (44.3 vs 33.5 ml kg^{-1} min^{-1}, $p = 0.031$) in addition to improved QoL ($p = 0.003$) and mental health scores ($p = 0.012$). The cardiovascular risk profile was similar in both groups aside from significantly higher triglycerides in the present cohort.

Small efforts as early physiotherapy and increased focus on physical activity after pediatric renal transplantation have significant impact on cardiorespiratory fitness, QoL and mental health. The importance of physical activity should therefore be emphasized in follow-up programs.

Keywords: pediatrics, renal transplantation, physical activity, oxygen uptake, cardiorespiratory fitness, quality of life.

Introduction

Kidney transplantation is the preferred treatment for end stage renal disease (ESRD) as it restores renal function and improves quality of life (QoL) [1]. Advancements in immunosuppressive treatment and increased knowledge in the post-transplantation care over the last decades have led to improved graft survival [2]. Prior to transplantation, the patients are exposed to an increased burden of cardiovascular risk factors due to uremia, volume overload and other unfavorable physiological conditions associated with ESRD [3]. The prevalence of cardiovascular risk factors is reduced after transplantation, but still prevails and shortens the life expectancy [4,5]. Reducing the risk of cardiovascular disease (CVD) is therefore an important part in the follow up of the patients. Life-style modifications such as physical activity and dietary changes are of most importance in modifying cardiovascular risk factors [6].

Peak oxygen uptake ($VO_{2\ peak}$) is a validated method to measure cardiorespiratory fitness and inactivity generally results in low $VO_{2\ peak}$ [7]. In our previous study, the HENT 1 (HEalth after kidNey Transplantation) performed 2008-2009, we showed that children with a renal transplant had a significantly lower $VO_{2\ peak}$ than healthy children [8]. In addition, $VO_{2\ peak}$ was a predictor of QoL. These children had significantly impaired QoL and mental health as compared with healthy children and children previously treated for Acute Lymphoblastic Leukemia (ALL) [9]. As a consequence of these results, our post- operative transplant program was adjusted and now includes regular training with early incremental physiotherapy, and the importance of being as physically active as their healthy peers is continuously emphasized.

The primary aim of this study was to determine whether incremental physiotherapy and increased focus on physical activity during the post-transplant follow-up have a positive impact on cardiorespiratory fitness and traditional cardiovascular risk factors. A secondary aim was to determine whether implementation of increased focus on physical activity would have an impact on QoL and mental health.

Material and methods

Study subjects:

All children and adolescents (1-18 years) who had a renal transplantation in the period December 2000-April 2015 at Oslo University Hospital (OUS), the only transplant center in Norway, were invited to participate in a cross-sectional study, the HENT 2 study. The inclusion criterion was a functioning graft for at least one year. The study was carried out in conjunction with the annual routine check-ups at OUS. All patients went through an extensive program over one day that included a thorough physical examination, various medical investigations and completed standardized questionnaires regarding QoL and mental health. Patients older than eight years of age and without any musculoskeletal or orthopedic limitation were also invited to participate in a second investigation day (Day 2) including an exercise test (measurement of $VO_{2\ peak}$) and a twenty-four-hour ambulatory blood pressure monitoring (ABPM). Medical records were searched regarding patients' background information. Written informed consent was obtained from patients and/or their parents if younger than 16 years of age prior to study start. The study protocol was approved by the Regional Committee for Research Ethics and carried out in accordance with the Declaration of Helsinki.

Comparison group:

The group of children that participated in the HENT 1 study in 2008-2009 was used for comparison [8]. The HENT 1 group consisted of 38 children and adolescents (age 2-19 years) transplanted in the years 1993-2006. A subgroup of 22 children was tested on a treadmill and $VO_{2\ peak}$ was measured equivalent to HENT 2.

Intervention:

Starting in 2010 the post-transplantation physiotherapy protocol has been intensified resulting in the patients receiving physiotherapy regularly already 1-2 weeks after transplantation, with individualized increments in intensity (2-3 times a week or more). The physiotherapy-protocol is initiated while admitted in the pediatric ward after transplantation and continued in an out-patients settings until transfer to follow-up at a local hospital approximately 3 months after transplantation. In addition, at each check-up at the outpatient clinic, the children are encouraged to participate in sports and daily physical activities to the same extent as their healthy peers. The safety of physical activity and its importance in regards to prevention of CVD is continuously emphasized.

Anthropometrics:

Weight was measured to the nearest 0.1 kg and height and waist circumference was measured to the nearest 0.1 cm. BMI was calculated as kg/m^2. For weight, height and BMI Z-scores were calculated based on the LMS-method using Norwegian reference data [10]. Overweight and obesity was defined by using cut-off point as proposed by the International Obesity Task Force [11].

Exercise testing ($VO_{2\ peak}$):

The participants performed an incremental treadmill exercise test on a motor driven treadmill (Woodway PPS 55 Med, Woodway GmbH, Weil am Rein, Germany) using the Oslo protocol for testing of children. Oxygen uptake during exercise was measured using Jaeger Vyntus CPX (Carefusion GmbH, Höchberg, Germany). The participants were tested till exhaustion and the test was considered maximal if the following criteria were met; 1) the participant was unwilling to continue despite encouragement from test supervisor, 2) respiratory exchange rate (RER) exceeded 1.0, and 3) heart rate exceeded 90% of age-predicted value (220 bpm – age) . Oxygen uptake at peak effort ($VO_{2\ peak}$) was determined and presented in relation to body weight (ml min^{-1} kg^{-1}) and this was defined as cardiorespiratory (CR) fitness. The protocol is described in previous publications [12,8].

Renal function:

Glomerular filtration rate (mGFR) was measured by using a single injection of iohexol (0.6 grams to children under 2 years and 1.5 grams to children over 2 years) with blood sampling after 2 and 5 hours [13].

Biochemistry:

Venous blood samples were drawn after an overnight fast.

Twenty-four-hour ambulatory blood pressure monitoring (24 hr ABPM):

24-Hour ABPM was performed by using a validated portable oscillometric ambulatory blood pressure monitor (Oscar 2; SunTech Medical Instruments, Morrisville, NC, USA). Test approval criteria, sex, and height adjusted mean daytime 95th percentile (95thp) blood pressure thresholds converted to z-scores were analyzed according to Wuhl et al [14]. Hypertension was defined as average systolic blood pressure (SBP) or diastolic blood pressure (DBP) during night or day >95% or antihypertensive treatment.

Health Related Quality of Life (HRQoL), mental health and psychosocial functioning:

The Pediatric Quality of Life Inventory (PedsQL) 4.0 [15] was used to measure Health Related Quality of Life (HRQoL) in children and adolescents. The PedsQL, version 4 General Core scales is divided into two reports; a child self-report and a parent proxy-report that assesses parents' perceptions of their child's HRQoL. The two reports are identical and can be grouped into four domains: (1) Physical functioning, (2) Emotional functioning, (3) Social functioning and (4) School functioning. The inventory assesses how much of a problem different items have been during the past month and the results are transformed to a 0-100 scale where higher scores indicate better HRQoL. In addition to the four subscales, a Total Summary Health score and a Psychosocial Health score can be computed.

The Strengths and Difficulties Questionnaire (SDQ) was used to assess the mental and psychosocial health in children and adolescents [16]. The SDQ is a brief behavioral screening questionnaire consisting of 25 items in addition to a supplement on the impact of the difficulties for the child and family. There are five subscales: Emotional symptoms, Conduct problems, Hyperactivity, Peer problems and Prosocial behavior, with the first four adding up to the Total Difficulties Score. Subscores are generated for each subscale (range 0–10) with higher scores indicating more problematic attributes. A total difficulties score of ≥19 defines symptom "caseness" according to Goodman (www.sdqinfo.com) and adjusted to Norwegian cut-offs [17]. As such, a symptom score >90 percentile predicts a substantially raised probability of being diagnosed with a psychiatric disorder, and a score of 16–18 is defined as “borderline”, i.e., symptom score within percentile 80–90. There are similar versions for parents.

The SDQ and the PedsQL are described in more details in our previous publication [9].

Statistics:

All statistical analyses were performed by using SPSS, version 23. Due to a small number of patients that participated in “day 2” and a skewed distribution, non-parametric statistics was applied. Continuous variables are described as median (range). The strength of an association of two continuous variables with skewed distribution was measured by using Spearmans’ correlation. Difference between the medians of two continuous variables were analyzed by applying Mann-Whitney-Wilcoxon test. Multivariate linear regression was chosen for adjusted analyses between $VO_{2\ peak}$ and potential explanatory variables. Sex, “HENT 1 or HENT 2”, age at study point, mGFR and time since transplantation were evaluated as possible explanatory factors. As the groups that were used to compare QoL and mental/psychosocial health were larger and more normally distributed, these data are described in mean (SD) and parametric statistics applied. For these latter groups, a t-test was used to test for the difference between the mean of two continuous variables.

Results

53 out of 59 (90%) eligible patients were enrolled in the study. Twenty-five (47%) patients completed a full 2 day program (Figure 1). Of these, five patients did not fulfill the criteria for a valid maximal $VO_{2\ peak}$, resulting in a group of 20 patients that was compared with the group of 22 patients with a valid $VO_{2\ peak}$ from HENT 1.

Base line characteristics

Baseline data for the different groups are presented in Table 1. Whereas triglycerides were significantly higher and duration of dialysis was significantly longer in HENT 2 patients, the other parameters were not significantly different between the two groups. For the patients who had a valid $VO_{2\ peak}$, the higher triglycerides levels was the only significant difference.

The majority of patients in HENT 2 received a tacrolimus (TAC) based immunosuppression (n=47), combined with mycophenolate (n=29) and prednisolone (n=58). Cyclosporine (CsA) was used in seven patients and nine received everolimus (EVE). Azathioprine (AZA) was used by three patients. Aside from the absence of EVE, the immunosuppressive therapy in HENT 1 was similar as in HENT 2 with 25 receiving TAC, 13 CsA, 11 mycophenolate, 37 prednisolone and four AZA.

Exercise test

The children in the HENT 2 study achieved 79% (57-106%) of the expected $VO_{2\ peak}$ for age-matched Norwegian children [18]. In comparison, the children from HENT 1 only achieved 69% (35-96%) of expected values. The group from HENT 2 had significantly higher $VO_{2\ peak}$ ($p = 0.031$) and maximal heart rate ($p = 0.043$) than the group from HENT 1 (Table 2). The study group and mGFR were significantly associated with $VO2_{peak}$ in univariate analyses. In the multivariate analysis, including these variables in addition to sex, age and time since transplantation, study groups, time from transplantation and mGFR were all independent significant predictors of $VO_{2\ peak}$ (Table 3). When checking for independency we found no significant interactions between mGFR, sex and study groups. Only two of the patients had a valid $VO2_{peak}$ from both studies and those were included in the analyses. In each group there was one patient using an erythrocyte stimulating agent.

The results from the exercise test for the two groups are presented in Table 2 and Figure 2.

HRQoL, mental health and psychosocial functioning

As shown in Table 4, the patients from HENT 2 reported significantly better HRQoL as compared with the patients from HENT 1. The difference was significant for the Total Difficulties score, the Psychosocial health score and for two out of four domains; i.e. Emotional and Social functioning. In the proxy-report the difference was significant for the Social functioning domain.

In the SDQ child self-report the children from HENT 2 also reported better scores than the children from HENT 1. Both the Total difficulties score and the scores from two out of the four problems subscales (emotional problems and peer problems) were significantly better. In the proxy-report the subscale peer problems score was significantly better (Table 4).

The mismatch in the number of participants and the number of answered questionnaires is caused both by the fact that some of the questionnaires are not applicable to young ages and that some of the participants did not return the questionnaires (8 patients in HENT 2). Up to ten patients had valid questionnaires from both studies.

Discussion

Our study indicates that a simple intervention such as early incremental physiotherapy and emphasis on physical activity at the same level as in healthy peers in our follow-up program after pediatric renal transplantation has a great impact on cardiorespiratory fitness, health related quality of life and mental health.

Children with chronic kidney disease (CKD), and especially those with ESRD, have limited exercise capacity compared with healthy children [19,20]. Factors such as physical inactivity, cardiovascular dysfunction, anemia, muscular limitation and neurodevelopmental abnormalities contribute to the poor exercise capacity and programs that intend to increase physical activity in children with CKD are often unsuccessful with a high dropout rate [21]. The most common reason for limited activity before transplantation in children with ESRD is fatigue/illness [22].

Several studies have shown CR fitness to be reduced in children and adolescents with a renal transplant as compared with healthy controls [23,20,24,25,8]. Lubrano et al have shown that 3-5 hours of physical exercise per week results in better CR fitness compared to 0-3 hours per week in a small group of children with a renal transplant. By exercising 3-5 hours a week the transplanted children could achieve a CR fitness comparable to healthy controls with a sedentary lifestyle and to children with congenital solitary kidney and a sedentary lifestyle [26,25].

After transplantation the children can adapt a different lifestyle with more energy to participate in physical activities. This can be challenging and frightening not only for the children who might be used to have fatigue as an excuse for being inactive, but also for the primary caregivers. Interestingly, Wolf et al [22] did not find longer duration of CKD before transplantation to be a significant risk factor for reduced activity after transplantation, suggesting that even patients with a short period of CKD before transplantation struggle with normalizing physical activity after transplantation.

The dominant reason for limited activity and participation in sport after transplantation is a “fear of kidney injury” [22]. Limited data exists on the safety of exercising after transplantation and there is no consensus or accepted guidelines for advising kidney transplant recipients about the risk of sport participation. In a study [22] on 101 young transplant recipients (7 – 21 years old), only three patients had an injury to the kidney due to an physical activity (of which none needed hospitalization) over the study period, which resulted in 0.007 allograft injuries per patient year of transplant follow-up. Participation in extreme endurance sports such as a long distance cycling also seems to be safe in regards to kidney function and protein- and microalbuminuria [27]. Even though evidences on safety in participation in physical activity after renal transplantation are scarce, it is tempting to assume that most physical activity is safe after transplantation, although most physicians would discourage sports with a high risk of direct injury to the abdomen such as kick-boxing and rugby.

The only significant difference in baseline characteristics and cardiovascular risk factors in this study was that the patients in HENT 2 had significantly higher triglycerides than the patients in HENT1. mTOR-inhibitors (mammalian Target Of Rapamycin inhibitor) such as everolimus are known to cause hypercholesterolemia and hypertriglyceridemia [28]. Over the last years the mTOR inhibitors have been used increasingly for our transplant patients and that might contribute to the high triglycerides levels in HENT 2, even though only 9/53 (17%) were on mTOR inihibitors. Different dietary habits might also explain this but we do not have any data on dietary habits in our patients. In a meta-analysis on the effect of exercise training in adult solid organ transplantation patients the authors found an improvement in oxygen-uptake but not in other cardiovascular risk factors as blood pressure, lipid profiles and glycemic control which is in concordance with our study. The reason for this might be short observation time.

The present study showed that the children from HENT 2 reported superior HRQoL than the children from HENT 1. One previous study has revealed a positive association between HRQoL and physical activity after transplantation measured by a pedometer, but in that study there was no association between self-reported activity and HRQoL [29]. Unfortunately, we don’t have any data on physical activity for these children that would strengthen the association between our informal intervention and HRQoL.

Decreased HRQoL is often associated with low socioeconomic factors [30]. We have limited data on our patients' socioeconomic status to rule out this as a confounder in our results. There have however, not been any major changes in the Norwegian society during the years between HENT 1 and HENT 2 that would explain any significant differences in the two groups. In addition, the socioeconomic status is relatively stable with few families in either high or low socioeconomic groups and with a participation of 90% in the study we assume that the study group represents the population quite well.

There is increasing evidence that physical activity [31,32] and improved cardiorespiratory fitness [33] have positive effect on children's mental health. A two year follow-up study on Australian children where SDQ was used revealed more psychological difficulties in those children that did not participate in sport or dropped out of sport participation during the follow-up [34]. These results in healthy children are in concordance with our findings in children with a history of a renal transplantation that improved cardiorespiratory fitness results in improved mental health. Interestingly, the children reported far better HRQoL than the parents, as has been reported in other studies [35-37].

Strengths and limitations:

The major limitation to our study is a small sample size. Never the less, it is a population based study as all children in Norway are transplanted and followed up at Oslo University Hospital and the participation rate was high (90%). In this cross-sectional study we compare two groups that are similar in most aspects at two different points with 7 years between them. To our knowledge, no other centers have reported on CR fitness and HRQoL after pediatric transplantation at two different times.

Another limitation is the lack of a standardized intervention. The intervention was not formalized by protocol but based on intensified post-transplantation physiotherapy and strong recommendations to the patients and care-givers both pre- and post-transplantation and at annual check-ups.

Another selection bias was that participants got to decide whether they participated in the full 2 days program or skipped the second day, including the exercise testing. Patients that are doing well physically might be more willing to participate in the exercise testing even though we found no significant difference in body composition or other baseline characteristics.

The peak heart rate was lower in the HENT1 than the HENT2 study. This could be due to a lower effort or lack of motivation in the HENT1 compared to the HENT2 study. However, there was no difference in the RER between the groups and the criteria for a maximal test was equivalent in both studies so this is not so likely.

At last but not least, a major strength is that no other changes have been made in our follow-up program that could explain this improvement in HRQoL and mental health, as even the nurse and doctor staff were unchanged since the HENT 1 study.

Conclusion

With our study we have demonstrated that more focus on physical activity and physiotherapy in the postoperative transplantation program combined with sustained encouragement on follow-up visits to stay physically active and participate in sports, is likely to have a great impact on CR fitness and to improve QoL and mental health. Physical activity plays an important role in preventing CVD. The risk of CVD is high in renal transplanted patients and therefore prevention of this is of particular importance in the follow-up of these patients. This must be taken into account when planning follow-up programs after pediatric renal transplantation.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Figure 1

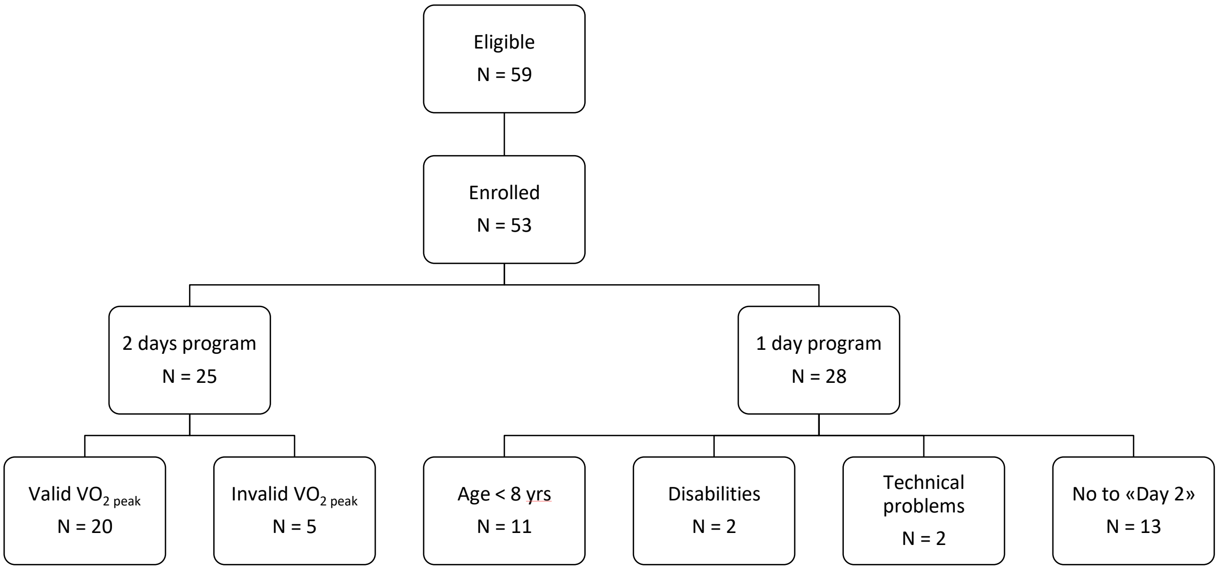
Eligible
N = 59
Enrolled
N = 53
2 days program
N = 25
1 day program
N = 28
Valid $VO_{2\,peak}$
N = 20
Invalid $VO_{2\,peak}$
N = 5
Age < 8 yrs
N = 11
Disabilities
N = 2
Technical problems
N = 2
No to «Day 2»
N = 13

Figure 2

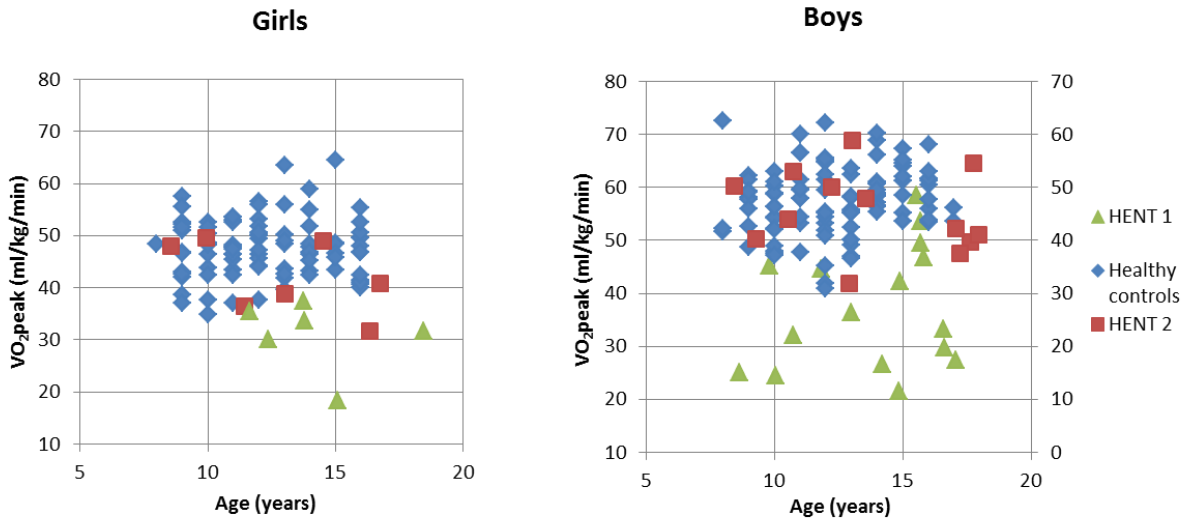
Girls
80
70
60
50
40
30
20
10
VO2peak (ml/kg/min)
5
10
15
20
Age (years)
Boys
80
70
60
50
40
30
20
10
VO2peak (ml/kg/min)
70
60
50
40
30
20
10
0
5
10
15
20
Age (years)
HENT 1
Healthy controls
HENT 2

Figure 1 Flowchart over participation in HENT 2

Figure 2 Comparison of $VO_{2\ peak}$ in HENT 1 and HENT 2 including healthy controls from HENT 1.

A.B., H.T. and A.L. designed the study. A.B., H.T., A.L. and T.T. collected the data. H.T., A.B. and T.H.D. analyzed the data and wrote the manuscript. All authors critically revised the manuscript.

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Table 1 Baseline characteristics for HENT 1 and HENT 2 and the groups from HENT 1 and HENT 2 with a valid $VO_{2\ peak}$. Values reported as median (range). Tx = transplantation.

				Treadmill groups		
	HENT1 N = 38	HENT 2 N = 53	P-value	HENT 1 N = 22	HENT 2 N=20	P-value
Age at day of study (years)	13 (3-19)	12.2 (2.3-18.0)	NS	14.5 (8.6-18.5)	13.0 (8.4-18.0)	NS
Age at Tx (years)	6.6 (0.8-15.7)	4.4 (0.8-15.8)	NS	7.5 (1.1-14.2)	6.2 (0.8-15.8)	NS
Time since Tx (years)	4.9 (2.0-16.0)	5.0 (1.0 - 15.5)	NS	5.2 (2.3-15.9)	4.9 (1.9-15.5)	NS
Male/female, (n)	25/13	32/21		16/6	13/7	
Living donor, n (%)	34 (89%)	48 (91%)		19 (86%)	16 (80%)	
Preemptive Tx n (%)	20(53%)	25 (47%)		13 (59%)	10 (50%)	
Duration of dialysis (months)	4.5 (1-15)	9.5 (0.25-39.5)	<0.001	4.0 (1-15)	6.2 (0.25-15)	NS
BMI (kg/m2)	19.2 (14.6-36.9)	17.9 (14.2-35.4)	NS	21.1 (15.7 - 36.9)	18.5 (16.1-32.11)	NS
BMI Z-score	0,58 (-2,79-3,57)	0.34 (-1.49-2.97)	NS	0.41 (-2.78-3.57)	-,01 (-1,49-2.97)	NS
Overweight/obesity (%)	8/5 (21/13)	12/5 (23/9)		4/4 (18/18)	2/3 (10/15%)	
Hypertension, ABPM (%)				16 (73%)	15 (79%)	
mGFR (ml/min/1.73m^2)*	51 (22-95)	56 (24-111)	NS	49.5 (22-77)	63 (33-105)	NS
Hemoglobin (g/dL)	12.1 (10.2-15.8)	12.2 (7.1-14.8)	NS	12.1 (10.2-15.6)	12.8 (9.5-14.8)	NS
Cholesterol (mg/dl)	161 (65-294)	162 (85-263)	NS	159 (35-186)	154 (119 - 216)	NS
Triglycerides (mg/dl)	89 (35-203)	159 (44-345)	<0.001	80 (35-186)	159 (71 -345)	<0.001
HDL (mg/dl)	54 (27-97)	54 (19-104)	NS	54 (31-96)	48 (35-81)	NS
LDL (mg/dl)	87 (39-189)	97 (23-197)	NS	91 (54-159)	85 (65-143)	NS

*for three patients from HENT 2 was GFR too low for measuring with a blood sample after 5 hours and in these instances is GFR estimated from creatinine

Table 2 Exercise test results from HENT 1 and HENT 2. Values reported as median (range).

	HENT 1 (N=22)	HENT 2 (N = 20)	p-value
Age (years)	14.5 (8.6 - 18.5)	13.0 (8.4-18.0)	NS
$VO_{2\ peak}$ (ml kg^{-1} min^{-1})	33.5 (18-59)	44.3 (31.7-58.8)	0.031
RER	1.1 (1.02-1.2)	1.12 (1.02-1.22)	NS
Maximal heart rate	183 (136-207)	193 (155-210)	0.043

Table 3 Multivariate linear regression model of cardiorespiratory fitness (ml/kg/min) in renal transplanted children. $R^2 = 0.39$.

Variables	Unstandardized Coefficient B	95% confidence interval for B	P-value
mGFR (mL/min/1.73 m^2)	0.22	0.06-0.38	0.009
Study group (HENT 1 vs. 2)	6.52	0.86-12.18	0.025
Time from transplantation (years)	0.83	0.06-1.59	0.034
Sex	4.38	-1.43-10.20	0.135
Age at study point (years)	- 0.09	-1.02-0.85	0.854

Table 4. Health related quality of life (HRQoL), mental health and psychosocial functioning of children with kidney transplantation at HENT 2 compared to HENT 1. Values reported as mean (SD).

	HENT 1	HENT 2	p-value
PedsQL child self-report	n=30	n=40	
Total score	69.10 (17.98)	80.56 (12.61)**	0.003
Psychosocial health	67.03 (18.05)	79.16 (12.24)**	0.002
Physical Functioning	74.89 (17.01)	81.51 (16.04)	NS
Emotional Functioning	69.48 (15.81)	80.38 (17.56)**	0.009
Social Functioning	73.71 (21.54)	87.13 (12.85)**	0.002
School Functioning	63.10 (17.75)	69.74 (16.74)	NS
PedsQL care-giverproxy-report	n=32	n=45	
Total score	68.37 (19.17)	71.65 (15.90)	NS
Psychosocial health	67.68 (18.93)	70.98 (15.65)	NS
Physical Functioning	69.36 (23.05)	72.64 (20.90)	NS
Emotional Functioning	70.00 (21.36)	72.22 (18.85)	NS
Social Functioning	67.79 (27.07)	79.00 (16.98)*	0.029
School Functioning	62.90 (23.16)	61.99 (20.61)	NS
SDQ child self-report	n=26	n=30	
Total difficulties	11.58 (5.69)	7.80 (5.16)*	0.012
No.(%) caseness; 19-40	2 (8)	0 (0)	
No.(%) borderline; 16-18	6 (23)	1 (3)**	0.006
Emotional problems	3.62 (2.10)	2.23 (1.76)	0.01
Conduct problems	1.85 (1.64)	1.27 (1.26)	NS
Hyperactivity problems	3.58 (2.18)	2.87 (2.59)	NS
Peer problems	2.54 (2.16)	1.47 (1.33)*	0.027
Prosocial behaviour	7.89 (2.05)	7.97 (2.08)	NS
SDQ care-giver proxy-report	n=31	n=43	

Total difficulties	10.74 (6.30)	8.26 (5.60)	NS
No.(%) caseness; 19-40	4 (13)	2 (5)	
No.(%) borderline; 16-18	3 (10)	3 (7)	NS
Emotional problems	2.68 (1.97)	2.07 (1.89)	NS
Conduct problems	1.81 (1.54)	1.70 (1.55)	NS
Hyperactivity problems	3.68 (2.50)	2.93 (2.16)	NS
Peer problems	2.58 (2.49)	1.56 (1.78)*	0.043
Prosocial behaviour	7.81 (2.15)	8.07 (1.80)	NS